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Development of an Integrated Toxicity Assessment System for use in Operational Deployment and Materials Development

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Rapid assessment of chemical hazards and potential toxicity are serious concerns for the modern battle field commander before and following deployment. Whether it is considered during the design and development of a weapon system, or in the fielding of that system, the effects of chemicals used in operational setting have the potential to cause mission degradation, morbidity and mortality. In addition to NBC concerns, there are issues in many current military settings for exposures to toxic industrial chemicals or materials (TICs or TIMs). Significant health issues caused by use of legacy chemicals have emphasized the need for more effective predication of chemical toxicity. This paper discusses issues relating to toxicity predictions and the development of an integrated computational system for the assessment of chemical toxicity. The system design is comprised of a series of modules each dedicated to addressing specific areas of concern, e.g. exposure scenarios and chemical property predictions. The integrated toxicity assessment system (ITAS) is serving as a model for other industrial applications.

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TABLE OF CONTENTS

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1 Summary

Rapid assessment of chemical hazards and potential toxicity are serious concerns for the modern battlefield commander before and following deployment. Whether it is considered during the design and development of a weapon system, or in the fielding of that system, the effects of chemicals used in operational settings have the potential to cause mission degradation, morbidity and mortality. In addition to NBC concerns, there are issues in many current military settings for exposures to toxic industrial chemicals or materials (TICs or TIMs). Significant health issues caused by use of legacy chemicals have emphasized the need for more effective prediction of chemical toxicity. This paper discusses issues relating to toxicity predictions and the development of an integrated computational system for the assessment of chemical toxicity. This novel system is designed to incorporate diverse data types. Hazardous agent sensor data, literature or database information, biotechnology data, in vitro/in vivo toxicity assessments, and computational chemistry parameters will be used in evaluating the possible level of chemical toxicity risk associated with operational use. The system design is comprised of a series of modules each dedicated to addressing specific areas of concern, e.g. exposure scenarios and chemical property predictions. The integrated toxicity assessment system (ITAS) is serving as a model for other industrial applications and has the potential to assist in both mission planning and materials development.

2 Introduction

In the interest of protecting the men and women who serve in the armed forces, it is important to effectively assess the potential hazards associated with chemical/material exposures. Chemicals are used throughout many fields of expertise and are not limited to maintenance or deployment situations. The purpose of this paper is three-fold: 1) Address the need for evaluation of chemical hazards in operational situations, 2) Discuss the current and emerging technologies available for toxicity prediction, and 3) Present the details of the Integrated Toxicity Assessment System (ITAS) approach.

3 The Need for Chemical Hazard Evaluation

Military operations place individuals in contact with chemicals and materials that may be different from those in their normal base settings (Kirkpatrick et al., 2002). Additionally, the exposure durations and levels may vary. Even in modern operations that utilize high-production volume chemicals, some toxicity questions still exist (Urbansky, 2002). So, it is important to have access to a sufficient amount of toxicity information before individuals are exposed to suspect compounds. One primary driver for this effort is to avoid the necessity for after-action responses to chemical hazards (Kramarova, 1998).

There are no "unmanned" weapon systems. Chemical exposures may occur during the manufacture, fielding, maintenance, or operation of a weapon system. Significant consequences may arise from ineffective assessment of chemical toxicity from those systems or from environments into which personnel are placed. Real-time, military operations may be restricted, in response to unforeseen chemical hazards, which may or

may not be mitigated. The concerns do not end with cessation of operations, but follow-on issues may arise from after-action health impacts (Knudson, 2002).

US Air Force concerns relate to both general occupational health as well as specific scenarios in deployed operations. Operational TIC/TIM exposures in deployed settings may occur with chemicals not held in the current military inventory, but are strictly industrial in nature. Obviously, these concerns go beyond those involved with a typical weapons systems life cycle (Aizenberg, 2000).

There are three basic areas where chemical/material toxicity should be assessed: 1) Materials development, 2) Weapon system integration, and 3) Deployed operations.

3.1 Materials Development

Chemicals and materials are designed by engineers and scientists to perform certain functions. These functions are characterized by various physical/chemical properties. For instance, a fuel must provide a certain amount of energy upon oxidation. Biological properties of chemicals are just as intrinsic as their physical/chemical properties. Therefore, while certain performance characteristics are selected for, so can minimizing potential toxic effects. As part of the development of a chemical/material, the potential impact on the military users must be considered. Effective up-front toxicity evaluations may help in avoiding legacy problems with chemicals. It is important to understand that toxicity evaluations at this juncture should not be considered "testing", but that these assessments are a fundamental part of the materials development process.

3.2 Weapon System Integration

Although chemical toxicity should be considered in the material development process, it is likely that chemicals selected for particular engineering solutions may still carry hazards that would be of concern. In a sense, toxicology is not a "gatekeeper", but a guide. Yet, it is important to have useful toxicity information in hand when weapon systems are designed and built. Engineers must consider the potential for human exposure to materials used in those systems. The outcome of proper precautions is the maximizing of weapon system performance while preventing mission degradation from chemical exposures during system operations.

3.3 Deployed Operations

The ubiquitous nature of chemicals requires that occupational health precautions do not cease during deployed operations. Appropriate consideration of potential chemical exposures increases mission planning effectiveness. Effective planning allows for more effective handling of hazardous materials.

4 Current and Emerging Technologies

The technologies available for toxicity assessments focus on three general areas: toxicity databases, quantitative structure activity relationships (QSARs), and expert systems. Although significant effort has been put into development of toxicity prediction tools, there are a number of unmet challenges. For instance, good tools for metabolism prediction are just now coming of age. For many software packages, especially QSAR-based approaches, there is little useful information that the user can obtain that provides insight into mechanisms of action. Often, a tool is required for providing insight to hypothesis generation concerning the toxicity mechanisms of a chemical.

4.1 Databases

Various U.S. and international groups maintain databases of chemical toxicity information (Felsot, 2002; Winter, 2002; Wolfgang and Johnson, 2002). With current technology, many of these can be accessed via the Internet and may not require a fee-based subscription. Some databases have comprehensive toxicity information, while others focus on single endpoints, e.g. carcinogenic

potential. However, there is one glaring problem, a unified query tool is lacking that would provide access to all of these disparate repositories. Of note among these databases are: IRIS (www.epa.gov/iris), primarily a human health risk database, IUCLID (ecb.ei.jrc.it/IUCLID), an EU sponsored effort covering the >2000 high production volume chemicals, and RTECS (www.cdc.gov/niosh/rtecs.html), which covers >150,000 chemicals. One emerging database project is called DSSTox, a distributed structure-searchable toxicity public database network. This is an effort lead by the US EPA (Richard and Williams, 2002). Finally, various consortia have formed, which are addressing the issue of genomic and proteomic data.

4.2 Structure-Activity Relationships (SARs)

SARs are mathematical models describing the correlation of biological activity of a chemical to its descriptors (i.e. properties). They may be quantitative in nature (hence the term Q-SAR) or simply descriptive. These models generally describe a single toxicity endpoint, e.g. carcinogenicity or skin sensitivity. Often, very good correlations (>0.95) can be identified between these endpoints and certain chemical descriptors, e.g. molecular orbital energy (Geiss and Frazier, 2001). However, single QSARs do not solve many problems and the highly specific nature basically prevents them from being applied to other endpoints of interest. Significant drawbacks are associated with QSARs: 1) Operational chemicals are often outside of the predictive space of these highly specific models, 2) Many QSARs are built from large pharmaceutical chemical databases, 3) Correlative QSARs provide little mechanistic insight required for risk assessment.

4.3 Expert Systems

Some rules-based applications exist for chemical toxicity evaluation. Their utility for toxicity "prediction" is limited, since the systems are generated upon previously identified toxicity identifiers. Some of the expert systems are useful because their rule-sets may be updated to reflect more current toxicity knowledge (Viswanadhan et al., 2002).

4.4 Metabolism

Although this paper has apparently focused on the potential toxicity of a particular operational chemical, it is important to understand that in a biological system, a chemical (the parent) may undergo modification or metabolism (Ekins et al., 2002). It may be the metabolite that is actually the culprit that interacts with biomolecules to cause the toxicological effect. Hence, for effective toxicity evaluations, the professional toxicologist must consider the production and activity of potential metabolites. Commercial computational tools are even more lacking in the area of metabolism prediction. Most of the software packages have models based on non-mammalian systems. Only one is known to have a significant complement of human metabolic information.

5 The Integrated Toxicity Assessment System (ITAS) Approach

The basic approach of ITAS is to take advantage of diverse, multi-media toxicity information available from internal or external databases and maximize the leverage that can be gained from commercial computational solutions. ITAS is an integrated software tool that incorporates elements of artificial intelligence and rules-based decision-making approaches to arrive at toxicity predictions with certain estimates of confidence. A far-reaching goal is to have the ability to integrate exposure and toxicity to predict occupational scenario-specific outcomes.

5.1 Biomolecular Profiling and Toxicity Fingerprinting

With the advent of genomic, proteomic, and metabonomic (GPM) techniques, the contemporary toxicologist has the potential to gain valuable insight into the mechanisms of chemical toxicity. However, the tools for dealing with this GPM information have not kept pace with the production of the information. Bioinformatics is key for distilling out the pertinent elements of the molecular response to toxic exposures.

The molecular response must be considered in light of other toxicity information, e.g. cellular status and dose-response relationships. These basic pieces of toxicity data comprise the "toxicity fingerprints" that are linked to the biomolecular profile based on GPM data.

5.2 ITAS Design

5.2.1 Toxicity Evaluation Module (TEM)

The TEM is the core of the ITAS system. One of the primary roles of this module is to interface with the user. The TEM will accept the chemical queries for the compounds/materials of interest and parse the toxicology questions. The TEM will act as a governor to determine the relevant databases to be accessed for data. The data from external sources, as well as experimental and computational information will be used for the assessment of toxicity potential. The TEM will provide the confidence levels associated with the toxicity reports. The toxicity reports will identify the pertinent endpoints of interest, e.g. single dose acute toxicity, skin irritation, or target organ toxicity.

5.2.2 Database Module (DM)

The DM will maintain the list of data sources, both internal and external. The DM tools will be able to automatically collect data from desired locations. The collected information will be condensed for transfer to the TEM for analysis by processing to a standard ITAS data format.

5.2.3 Computational Module (CM)

Many physical/chemical properties can be accessed from databases. However, in the event that a property, e.g. a lipid partition coefficient, is unavailable, the property will have to be calculated. This will occur in the CM. The CM will also analyze chemical structures to identify "related" chemicals that can be used as surrogates in toxicity profiling. In addition, the CM will identify chemical moieties that are related with particular types of toxic mechanisms.

5.2.4 Predictive Module (PM)

The PM is the module that will link with available computational toxicology tools and predictive models. QSAR data is catalogued in various locations and may be accessed for incorporation into ITAS predictions. Furthermore, the estimates of the kinetic, e.g. organ distribution, of the chemical will be performed in the PM.

5.2.5 Site-Specific Exposure Estimator Module (SSEEM)

Functions of the SSEEM include the evaluation of the dispersal of chemicals in the environment, behavioral patterns of target populations, and providing exposure estimates for target populations given specific operational scenarios.

5.3 Science and Technology Challenges

During the development of the ITAS product there are a number of scientific and technical challenges that must be addressed. Given the potential that many of the query chemicals may belong to unique classes of chemicals, it may be difficult to identify related compounds. Additionally, how one defines similarity can impact the usefulness of the flagged surrogates. Although computational chemistry has advanced significantly over recent years, the development of chemical descriptors has not focused on identification of those that are most related to toxicological activity. This has been left primarily for the toxicologists to accomplish. The toxicology knowledge base is a very fluid entity. Constantly, new information is gained concerning the toxicity of a chemical or class of chemicals. It is important for the ITAS system to be able to take advantage of the most current information. The behavior of chemicals in a biological system, e.g. its

biokinetic behavior, remains an important element of the toxicity evaluation of a chemical. One must determine the metabolism and target organ dosimetry in order to perform effective risk assessments. A significant, but mostly neglected, factor of human toxicity is the potential for genetic variation among a population that results in a segment of the population being more or less susceptible to experiencing toxic effects from a particular chemical. This inter-individual variability is a major factor when extrapolating from animal-based toxicity information to human risk assessment (Lamba et al., 2002).

6 Conclusion

The integrated toxicity assessment system (ITAS) serves as a model for other industrial applications and has the potential to assist in both mission planning and materials development. In the development process, ITAS can assist in "smart" chemical design. Comprehensive chemical toxicity assessments can aid in the engineering of weapons systems and establishment of personal exposure standards for operational environments. Finally, chemical/material toxicity information may be used in mission planning to aid in mission degradation avoidance and reduction of the potential for after-action health concerns.

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